Assessing Differential Drug Effect

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Abstract

The regression effect gives a misleading impression of the relation between drug or treatment effect and baseline measurement. We propose a method of adjusting for regression effect and a corresponding test for differential drug effect. These are illustrated using blood pressure data.

Key words: Differential drug effect, regression, regression effect, change from baseline, t tests.

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1. Introduction

A common method for assessing the effect of a drug or other treatment on a measurement is to compare baseline with postdrug, using each patient or subject as its own control. A test of the null hypothesis that the average difference is zero is carried out using a Student t test or a Wilcoxon signed-rank test. For efficacy measures a maximal effect may be desirable and for safety measures a minimal effect is desirable; while our methods apply to both, some of our discussion is presented in terms of the latter for convenience. In particular, our examples deal with blood pressure changes associated with an antiarrhythmic agent.

If there is an overall increase, say, between pre- and postdrug then the effect may be less important if the increase is less for patients with high baselines than for those with low baselines. One might test for differential effect of the drug by regressing change from baseline on baseline. In a similar vein, one might give average changes from baseline for low, middle, and high baseline values. One might feel that the drug is safer if the average increase for high baselines is less than it is overall. But such analyses are incorrect.

The problem is that an apparent differential effect may simply reflect a regression effect. Even if there is no drug effect whatever, patients with high baselines will tend to have lower second readings--these second readings will tend to be higher than average but lower than the corresponding baselines. In this paper we assume the joint distribution

of the two readings (or a suitable transformation) is normal and address the problem of removing the regression effect when the drug effect is additive. Based on this analysis we propose a simple test for differential drug effect. Examples are given in Section 4.

2. Regression and differential effect

Let X_1 denote baseline and X_2 the corresponding postdrug measurement. Assuming normality:

$$\begin{pmatrix} X_1 \\ X_2 \end{pmatrix} \sim N\left(\begin{pmatrix} \mu \\ \mu+\Delta \end{pmatrix}, \begin{pmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{pmatrix}\right) :$$

For the before/after data we have in mind the correlation coefficient ρ will usually be positive, but such an assumption is not necessary in what follows.

If there is no drug effect (or confounding time effect) then X_1 and X_2 will have the same marginal distributions: $\Delta = 0$ and $\sigma_1 = \sigma_2$. If the drug affects all patients additively and equally then $\Delta \neq 0$ and, again, $\sigma_1 = \sigma_2$. While there is no real differential drug effect in either case, there is an apparent one.

To see this, consider the joint distribution of baseline and change from baseline when there is an additive effect and $\sigma_1 = \sigma_2 = \sigma$:

$$\begin{pmatrix} X_1 \\ X_2 - X_1 \end{pmatrix} \sim N\left(\begin{pmatrix} \mu \\ \Delta \end{pmatrix}, \sigma^2 \begin{pmatrix} 1 & \rho-1 \\ \rho-1 & 2(1-\rho) \end{pmatrix}\right).$$

The regression function of $X_2 - X_1$ on X_1 is

$$E(X_2 - X_1 \mid X_1) = \Delta - (1-\rho)(X_1 - \mu).$$

The regression effect has an obvious impact on change from baseline; for example, subjects with large baselines (X_1) have smaller than average change from baseline. The regression effect can be removed (for purposes of plotting as well as further analysis) by considering

$$Y = X_2 - X_1 + (1-\rho)(X_1 - \mu) = X_2 - \mu - \rho(X_1 - \mu)$$

versus X_1. Since $E(Y|X_1) = \Delta$ when there is no differential drug effect, a nonzero slope of the regression of Y on X_1 indicates a genuine differential effect.

In the general model with σ_1 and σ_2 arbitrary,

$$E(X_2 - X_1|X_1) = \Delta + (1-\rho\theta)(X_1 - \mu),$$

where $\theta = \sigma_2/\sigma_1$. Also,

$$E(Y|X_1) = \Delta + \rho(\theta - 1)(X_1 - \mu).$$

The null hypothesis of no differential drug effect and its alternative are

$$H_0 : \sigma_1 = \sigma_2,\ H_1 : \sigma_1 \neq \sigma_2.$$

A differential effect--if one is present--is negative or positive corresponding to the sign of $\rho(\theta - 1)$.

Figure 1 illustrates this phenomenon with $\Delta > 0$ and $\rho > 0$; ellipses of constant bivariate normal density are shown. In Figure 1A there is no differential drug effect, $\theta = 1$. In Figure 1B there is a negative differential effect, $\theta < 1$; large baselines are increased less than small baselines. In Figure 1C there is a positive differential effect, $\theta > 1$; the figure was drawn with $\theta = \rho^{-1}$ which means there is apparently no differential effect in comparing $X_2 - X_1$ with X_1--it is masked by the regression effect.

[Figure 1 about here.]

3. Testing for differential effect

The maximum likelihood estimates of σ^2 and ρ under H_0 are

$$\hat{\sigma}^2 = (S_1^2 + S_2^2)/2, \qquad \hat{\rho} = rS_1S_2/\hat{\sigma}^2,$$

where S_1^2, S_2^2, and r are usual unrestricted maximum likelihood estimates of σ_1^2, σ_2^2, and ρ. The likelihood ratio test of H_0 vs. H_1 is

$$\text{Reject if } \left|\frac{S_1}{S_2} - \frac{S_2}{S_1}\right| \Big/ \sqrt{1-r^2} > K.$$

The null distribution of the test statistic is independent of ρ; in fact

$$(1) \qquad T = \frac{\sqrt{n-2}}{2}\left(\frac{S_1}{S_2} - \frac{S_2}{S_1}\right) \Big/ \sqrt{1-r^2}$$

has a Student t distribution with n-2 degrees of freedom where n is the sample size.

To see this, consider the transformation $U_1 = X_1 + X_2$, $U_2 = X_1 - X_2$;

$$\begin{pmatrix} U_1 \\ U_2 \end{pmatrix} \sim N\left(\begin{pmatrix} 2\mu + \Delta \\ \Delta \end{pmatrix}, \begin{pmatrix} \sigma_1^2 + \sigma_2^2 + 2\rho\sigma_1\sigma_2 & \sigma_1^2 - \sigma_2^2 \\ \sigma_1^2 - \sigma_2^2 & \sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma^2 \end{pmatrix}\right).$$

Testing $\sigma_1 = \sigma_2$ is the same as testing $\rho_{U_1,U_2} = 0$. Since U_1 and U_2 are jointly normal, the likelihood ratio test of $\rho_{U_1,U_2} = 0$ is the usual t test based on

$$T = \sqrt{n-2}\ r_{U_1,U_2} \Big/ \sqrt{1 - r_{U_1,U_2}^2}$$

which is algebraically equal to T as defined in (1). This test was derived originally by Pitman (1939) and Morgan (1939).

To summarize, the presence of an additive drug effect can be tested with the usual paired t test (assuming normality is not violated in an important way). The possibility that the drug affects patients differentially, depending on their baselines, can be tested using (1).

4. Examples

The method presented above is illustrated using diastolic blood pressure data from a recent multicenter clinical trial. (The Flecainide-Quinidine Research Group 1983.) This trial employed a randomized, double-blind design to compare two antiarrhythmic agents, flecainide acetate and quinidine sulfate, on the basis of efficacy and safety. There were seven days of placebo, after which baseline readings were taken, 14 days of active drug, and then seven days of placebo washout.

[Figures 2 to 5 about here.]

The washout data, using patients randomized to flecainide, provide an example in which there should be neither an additive nor a differential effect. Figure 2 shows the plot of change from baseline at washout vs baseline ($X_2 - X_1$ vs X_1). This clearly shows the regression effect. Figure 3 is the plot of these data after removing the regression effect (Y vs X_1), showing that there is no differential effect. The t test for additive effect gives $T = 0.80$, which is not significant. To test for differential effect, the t test described above gives $T = 0.55$, which is not significant.

The diastolic blood pressure data while on flecainide provide an example in which there may be an additive and also a differential effect. Figure 4 is the plot of change from baseline vs baseline ($X_2 - X_1$ vs X_1). There seems to be a small additive effect ($\hat{\Delta} = 3.1$ mmHg) for which $T = 3.50$ (very significant) and an apparent negative differential effect. Figure 5 shows the data after the regression effect has been removed. The t statistic for differential effect is $T = 0.84$, which is not significant. Evidently, the drug affects all patients in this population equally and additively.

While a casual analysis leads to one conclusion, a correct analysis leads to quite another.

Acknowledgement

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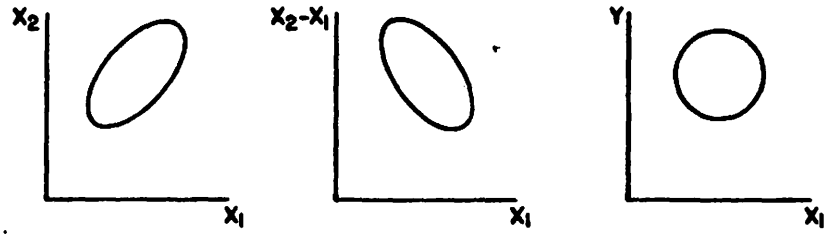
References

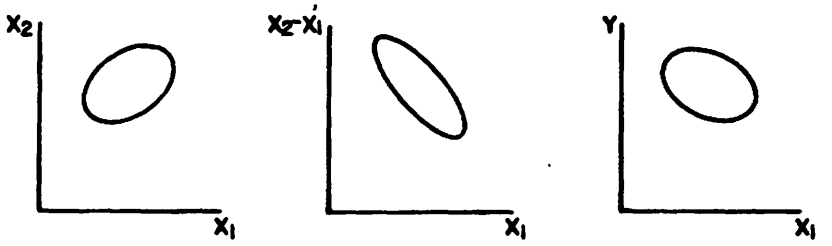
The Flecainide-Quinidine Research Group (1983). Flecainide versus Quinidine for treatment of chronic ventricular arrhythmias: A multicenter clinical trial. Circulation. (In press.)

Morgan, W.A. (1939). A test for the significance of the difference between the two variances in a sample from a normal bivariate population. Biometrika 31, 13-19.

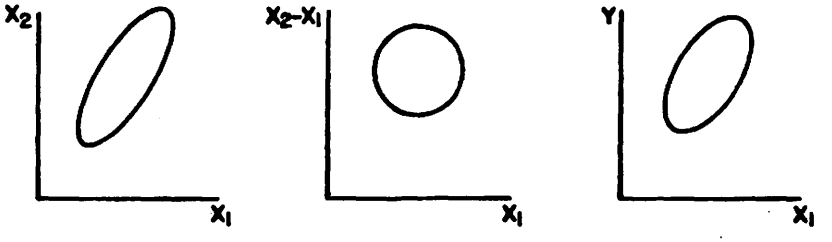
Pitman, E.J.G. (1939). A note on normal correlation. Biometrika 31, 9-12.



1A. No differential effect: $\theta = 1$ $(\sigma_2 = \sigma_1)$



1B. Negative differential effect: $\theta < 1$ $(\sigma_2 < \sigma_1)$



1C. Positive differential effect: $\theta > 1$ $(\sigma_2 > \sigma_1)$

Figure 1. Bivariate normal contours showing differential drug effect.

Figure 2

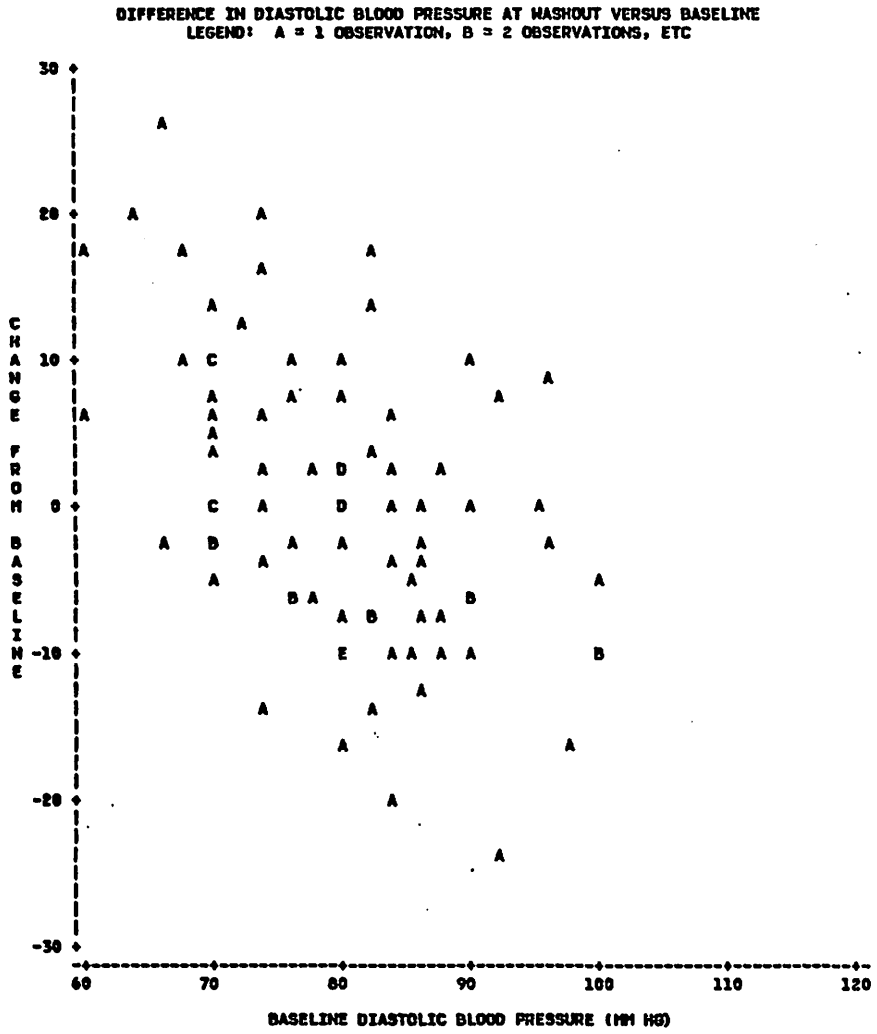


Figure 3

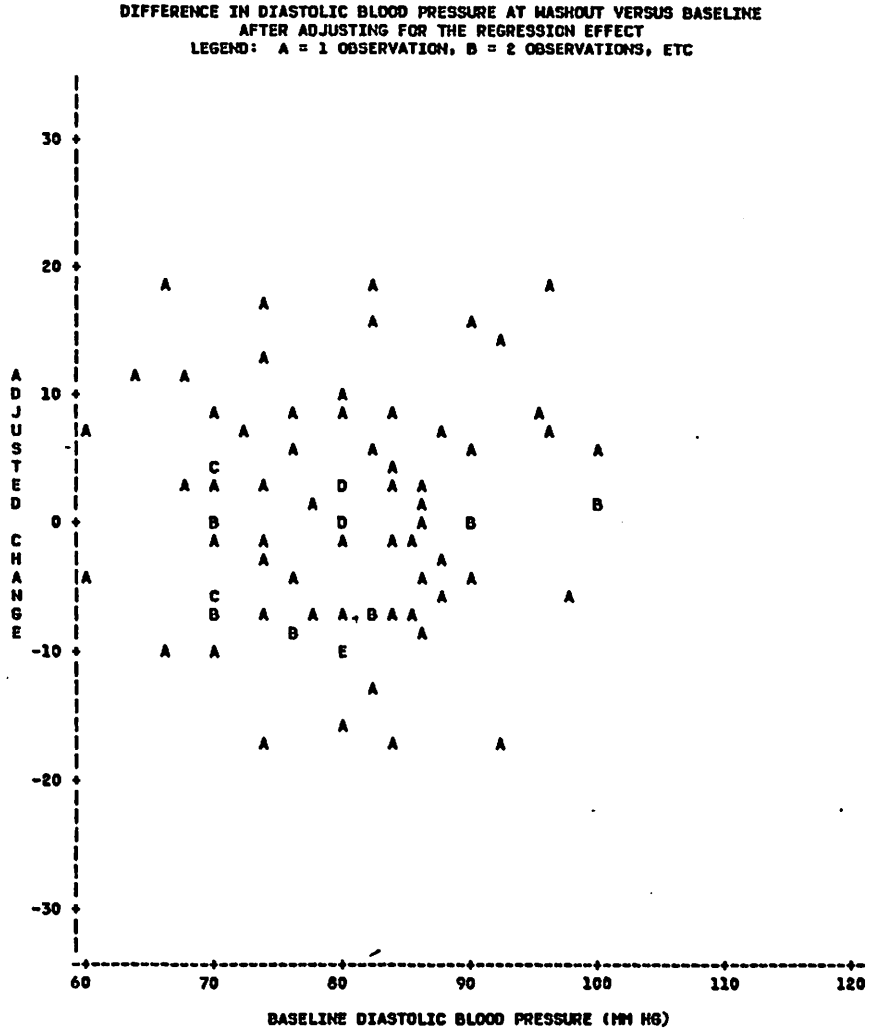


Figure 4

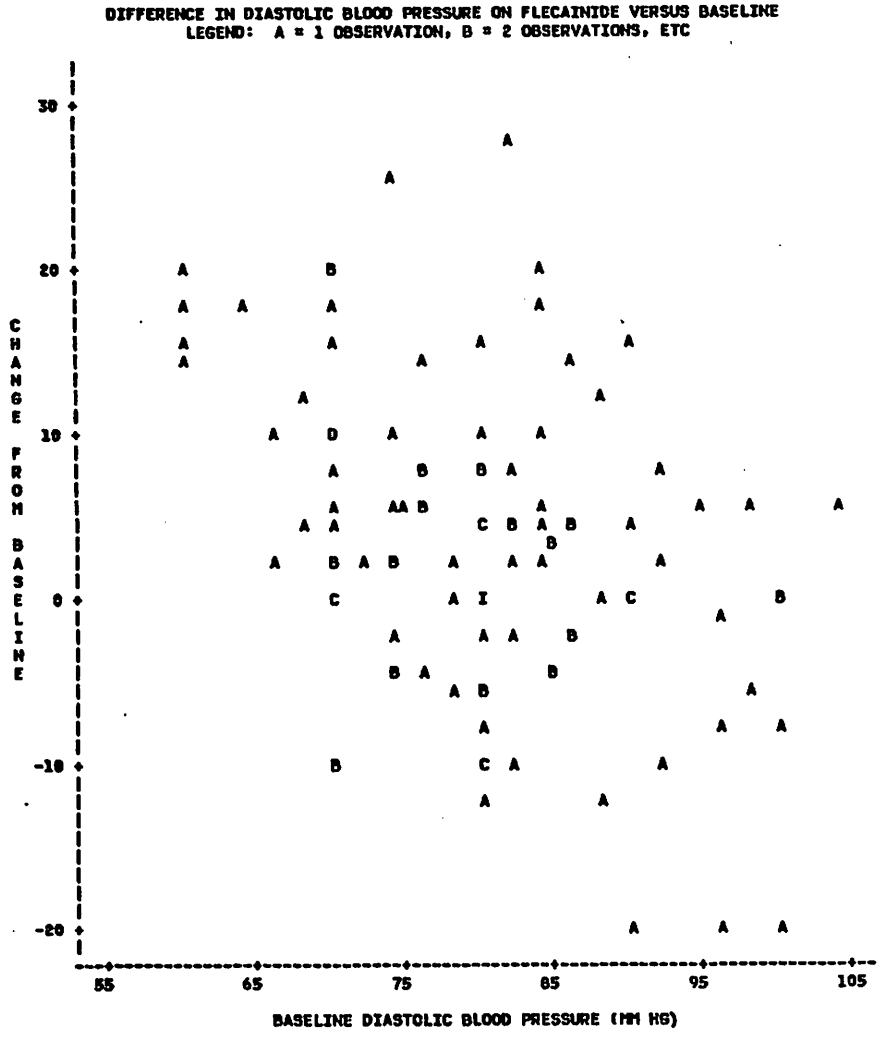


Figure 5